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(54) Title: OVULATION METHODS, DEVICES AND TEST KITS FOR MONITORING

(57) Abstract

A method of monitoring the status of a current ovulation cycle of an individual female mammalian (generally human) subject, involving repeated testing of the body fluid concentration of at least one analyte, preferably estrone-3-glucuronide (E3G) of significance in relation to the status of the ovulation cycle, during at least the pre-ovulation phase of the current ovulation cycle of the individual subject, wherein testing for said analyte concentration during the current ovulation cycle conducted at least once during the interval spanning days 1 to 7 inclusive following the onset of menses, to establish a reference concentration value for analyte in the current cycle, and then testing is conducted repeatedly during a plurality of days, preferably commencing at least 5 numerical days in advance of the mean numerical day on which actual ovulation has occurred over one or more previous ovulation cycles in the same individual subject, analyte concentration values obtained during said repeated testing being compared with the reference concentration value to determine whether a concentration change indicative of imminent ovulation is occurring or has occurred since the previous test. The method can be based solely on E3G measurements.

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OVULATION METHODS, DEVICES AND TEST KITS FOR MONITORING

This invention relates to methods, devices and test kits for use in monitoring the ovulation cycle in female mammals especially humans.

The invention is particularly, although not solely, concerned with simple practical procedures that can readily be applied by unskilled persons, e.g. in the home, to provide reliable information concerning fertility status as an aid to contraception. An important objective of the invention is to provide such information while avoiding the necessity for tests to be conducted on a frequent (eg. daily) basis throughout every ovulation cycle. The necessity for regular, e.g. daily, testing throughout the cycle has characterised many ovulation cycle monitoring systems previously proposed.

The invention may also be used by persons wishing to enhance the likelihood of conception, by providing an indication of the time during the ovulation cycle when fertilization is most likely to occur.

To provide reliable information concerning fertility status, the user must be given adequate warning of the onset of the fertile phase in the cycle. A wide variety of techniques have proposed in the art, some relying on the monitoring of one or more parameters which alter as the event of ovulation approaches. Typical parameters which have been invoked are the concentration of a body fluid analyte, such as estradiol and metabolites thereof, for example estrone-3-glucuronide (E3G). Other parameters that have been used are basal body temperature (which can only provide predictive information of use in subsequent cycles) and various physiological changes such as the characteristics of vaginal mucous.

Many excellent academic studies have been carried out using such parameters. Such studies have established how these parameters can be correlated with the fertility status of an average member of a large population sample. An example is Collins et al (1981), Proc. Xth International COngress on Fertility and Sterility, Publ MTP Ltd, p 19-33. An underlying objective in many such studies is to promote conception in individuals previously regarded as being infertile.

However, when attempting to develop a practical monitoring system suitable for use by individuals, it is found that many individual subjects do not conform to the average in terms of cycle length and/or the duration and timing of the fertile phase. The extent of variation from one individual to another, and indeed, from one cycle to another in the same individual, renders average population data too unreliable for consistent practical use.

Understandably, because the severe consequence of imperfect advice concerning fertility status may be an unwanted pregnancy, the tendency has been to exercise extreme caution and to require testing of the relevant parameter or parameters throughout the cycle, and particularly right from the onset of the cycle (onset of menses). From the individual user's point of view, it would be advantageous if the necessity for such constant testing could be avoided and, instead, for the testing to be performed over a comparatively brief portion of each cycle. Not merely may this benefit the user in terms of convenience, but the cost of the method may also be reduced if the method utilises disposable testing devices and only a few such disposable testing devices are required each month.

An example of a system for detecting the onset of ovulation, using water-swellable polymer pellets to "measure" the water content of vaginal mucus, whic,

apparently increases at the time of ovulation, is described in US 4151833 (Polishuk). It is stated that the peak variation in the size of the pellets, as a result of the absorption of water from cervical mucus, is closely related to the LH surge and the variation in basal body temperature. From the experimental data provided in US 4151833 (Figure 8), it appears that the pellet diameter is indeed very closely related to the timing of the LH surge, and in consequence the system proposed cannot in practice provide a reliable warning of the onset of ovulation earlier than that obtainable from a knowledge of the LH concentration.

In EP-A-385621 (Coley et al/Unilever) the defects of ovulation cycle monitoring systems which rely primarily on the change in BBT to estimate the time of ovulation are described, and we propose therein a system which uses regular BBT measurement in combination with a knowledge of other parameters, particularly the measurement of certain urinary hormone levels. A particular proposal is that BBT is measured daily throughout each cycle and is used to estimate the timing of fertility status changes in a forthcoming cycle. During the course of this forthcoming (predicted) cycle, urinary hormone levels are checked at certain times to confirm that the progress of the cycle, as predicted from the previous BBT knowledge, is consistent. Particular hormones selected are E3G, P3G and LH. It is suggested that the level of urinary E3G is measured on at least one day during the interval from day 5 to 7 of the predicted cycle, and again on at least one day during the interval from day 10 to day 15 of the predicted cycle. According to the example in EP 385621, it is sufficient for the hormone level to be either "high" or "low" relative to a threshold value. The emphasis throughout EP 385621 is that occasional hormone level measurements are used to supplement a monitoring system which relies on BBT measurement. There is no suggestion that hormone

measurements alone could provide the basis for a reliable fertility monitoring system personalised for an individual subject.

An objective of the present invention is to provide a system for monitoring the fertility status of an individual subject, which provides sufficient warning of the onset of the fertile phase to enable contraceptive advice to be given and which can be personalised to the individual subject, while being based solely on body fluid analyte measurements. The inherent unreliability, or limited usefulness, of other measuring systems (such as BBT) can thereby be avoided. A further objective is to avoid the use of average data obtained from population studies, with its inherent risk that in an individual subject, the parameter under test can fluctuate considerably from the population norm.

A further objective is to provide the option of basing an effective monitoring system solely on the measurement of a single body fluid analyte, such as estradiol or a metabolite thereof. Other advantages of the invention will be apparent from the following description.

Another objective of the invention is to provide a testing regime which is a good balance between the desire to minimise the testing burden on the user and the need to give the user worthwhile advice about the fertility status.

For the purposes of illustration only, the invention will be described in relation to the measurement of urinary analytes, and especially "E3G" (estrone-3-glucuronide) and "LH" (luteinising hormone).

In addition to estrone-3-glucuronide already mentioned, estradiol metabolites that can also be assayed for the purposes of the invention include estradiol-3-glucuronide, estradiol-17-glucuronide, estriol-3-glucuronide, estriol-

16-glucuronide and (principally for non-human subjects) estrone-3-sulphate. As will be appreciated from the following description, the invention can readily be applied to data derived from the measurement of body fluid concentrations of other analytes of significance in relation to the status of the ovulation cycle. Generally, the most suitable analytes are hormones and their metabolites. Follicle stimulating hormone (FSH) is an example. Examples of alternative body fluids, which are relatively accessible, are saliva, crevicular fluid, sweat, sebum, tears and vaginal fluid. In principle, internal fluids, such as blood, can be used but are generally not preferred because they can only be accessed by invasive techniques.

The skilled reader will also appreciate that the body fluid "concentration" of the chosen analyte or analytes need not be measured in absolute terms, although this can of course be done if desired. Generally, it will be sufficient to assay an analyte in a manner which yields a signal, convertible to numerical data, related to the actual concentration, so that such data can be compared with similar data obtained at a different stage in the cycle to determine whether or not a significant change in actual concentration has occurred. Accordingly, where the specification and claims below refer to the "concentration" of an analyte, this expression should be interpreted broadly.

The invention provides a method of monitoring the fertility status of an individual female mammalian subject, involving testing of the body fluid concentration of an analyte, especially estradiol or a metabolite thereof, in which method said testing is conducted at least once during the interval spanning days 1 to 7 inclusive of the current cycle, to establish a reference concentration value or signal for the current cycle, and said testing is also

conducted later in the current cycle and the concentration value or signal then obtained is compared to the reference value or signal.

An important aspect of the invention is a method of monitoring the current fertility status of an individual human female, involving testing of the body fluid concentration of estradiol or a metabolite thereof and comparing the test result with a reference value or signal to ascertain whether an elevated concentration indicative of imminent ovulation is present, wherein the reference value or signal for the current ovulation cycle is established by testing the body fluid concentration in the same individual at least once during the interval spanning days 1 to 7 inclusive of the current cycle.

More particularly, the invention provides a method of monitoring the current fertility status of an individual human female, involving testing of the body fluid concentration of estradiol or a metabolite thereof and comparing the test result with a reference value or signal to ascertain whether an elevated concentration indicative of imminent ovulation is present, wherein the reference value or signal for the current cycle is established by testing the body fluid concentration in the same individual at least once during the interval spanning days 4 to 7 inclusive, preferably on days 5 and/or 6, of the current cycle, testing is recommenced on day 9 of the current cycle and continued thereafter on at least a daily basis at least until a significantly elevated concentration is detected, and the status of the current cycle is declared to be "fertile" for the interval commencing on the day of significantly elevated concentration detection and for at least the immediately successive 12 days or until evidence of cycle termination (e.g. commencement of menses) is obtained, whichever occurs earlier. As an optional refiinement of this method, if a significantly elevated

concentration is not detected on or before day 15, the cycle is declared "fertile" for the interval lasting for at least 14, preferably 15, days immediately following day 15, or until evidence of cycle termination is obtained, if this occurs earlier.

Another important aspect of the invention is a human contraception method, involving:

a) testing the urinary concentration of estradiol or a metabolite thereof in the female partner at least once during the interval spanning days 4 to 7 inclusive, preferably on days 5 and/or 6, of the current cycle to establish a reference value or signal for the current cycle;

b) testing the urinary concentration again on an at least daily basis commencing on day 9 of the current cycle and continuing until day 15 (preferably day 14) of the current cycle; and

c) avoiding unprotected intercourse during the interval lasting for at least 12 days immediately following the day on which a significantly elevated urinary concentration is detected or, if a significantly elevated urinary concentration is not detected by day 15 (preferably day 14), avoiding unprotected intercourse during the interval lasting for at least 14, preferably 15, days immediately following day 15 (preferably day 14), in either case the interval optionally being terminated earlier in the event of evidence of cycle termination (e.g. commencement of menses) being obtained.

In a first embodiment, the invention provides a method of monitoring the fertility status of an individual female mammalian subject, involving testing of the body fluid concentration of at least one analyte of significance in relation to the status of the ovulation cycle during the pre-ovulation phase, wherein testing for said analyte is

conducted at least once during the interval spanning days 1 to 7 inclusive of the current cycle calculated from the onset of menses (day 1 being the day on which menstruation is first observed), to establish a reference concentration value or signal for said analyte in the current cycle, and thereafter testing is conducted at least once (generally repeatedly, e.g. daily) prior to a day on which ovulation is likely to occur during the cycle, analyte concentration values or signals obtained during said later or repeated testing being compared with the reference concentration value or signal to determine whether a concentration change indicative of imminent ovulation is occurring or has occurred since the previous test.

In a preferred embodiment, the invention provides a method of monitoring the fertility status of an individual female subject, involving testing of the body fluid concentration of at least one analyte of significance in relation to the status of the ovulation cycle during the pre-ovulation phase, wherein testing for said analyte is conducted at least once during the interval spanning days 1 to 7 inclusive calculated from the onset of menses (day 1 being the day on which menstruation is first observed), to establish a reference concentration value or signal for said analyte in the current cycle, and then testing is conducted at least once (generally repeatedly, e.g. daily) during a period of days commencing at least 5, and more preferably at least 6, numerical days in advance of the mean numerical day on which actual ovulation has occurred over one or more previous ovulation cycles in the same individual subject, analyte concentration values or signals obtained during said period of days being compared with the reference concentration value or signal to determine whether a concentration change indicative of imminent ovulation is occurring or has occurred since the previous test. Generally, the repeated testing need not be commenced earlier than about 9 days in advance of the mean

ovulation day.

Preferably, the concentration reference value is established from test(s) conducted during the interval spanning days 4 to 7 inclusive, more preferably from test(s) conducted on day 5 and/or day 6, and most preferably from a single test conducted on day 6.

A significant change in analyte concentration indicative of imminent ovulation, particularly appropriate when the analyte is estradiol or a metabolite thereof, will generally be noted when the ratio of the reference concentration [r] to the test concentration [i] meets the following criteria:

$$1.5 \leq \frac{[i]}{[r]} \leq 2.5$$

In particular, especially when the analyte is E3G and the reference value is established on day 6:

$$\frac{[i]}{[r]} \geq 2$$

If the chosen assay format by means of which concentration data is obtained yields a signal which is inversely proportional to actual concentration, as may be the case in a competition assay, it will be appreciated by the skilled reader that the relationship between [i] and [r] signals will be the inverse of those given above.

It is generally envisaged that there will be a gap of at least one day, and more usually several days, between establishment of the concentration reference value and the commencement of repeated testing, during which gap no testing need be conducted. Thus, in the ideal situation, the user performs a single test at an early stage of the cycle, eg on day 6, and several days later commences a

relatively brief schedule of repeated, eg daily testing, which is terminated after sufficient information has been derived to identify the fertile phase, preferably including an indication of the end of the fertile phase in that cycle. Typically this termination of testing will be on the day of LH surge, or within a few days thereafter, so that the remainder of the cycle is test-free.

Conveniently, the body fluid can be urine. A very suitable analyte is therefore estradiol or a metabolite thereof, such as estrone-3-glucuronide.

Preferably, in one embodiment of the invention, the mean ovulation day is derived from data collected during at least 3, and more preferably at least 5, consecutive previous cycles.

Ideally, the mean ovulation day used to calculate the time interval for the purposes of the current cycle is derived from data obtained during at least the immediately preceding cycle.

A particularly convenient method involves the determination of the mean ovulation day from data obtained from a "rolling" reference base consisting of a fixed number of consecutive cycles immediately preceding the current cycle. Preferably this rolling reference base consists of the immediately preceding 3 to 12 cycles, more preferably the immediately preceding 5 or 6 cycles. By having such a rolling reference base, any progressive "drift" in the occurrence of ovulation in the individual concerned can be picked up and accounted for in the allocation of the next repeated testing commencement day.

The invention includes a test kit comprising one or more testing devices for determining the concentration (in relative or absolute terms) of said at least one analyte in

said body fluid, together with instructions advising the user to commence said testing during said time interval, and means enabling a user to derive said time interval and/or a precise testing commencement day from knowledge of the numerical day on which actual ovulation occurred during at least one previous ovulation cycle of the user.

Another independent aspect of the invention, which may nevertheless be combined to advantage with any method as set forth above, involves:

a) providing the user with a plurality of disposable body fluid testing devices, said plurality preferably being at least 7, but preferably not greater than 12; and

b) directing the user to use all of said provided testing devices during a single ovulation cycle, in accordance with a predetermined testing schedule, irrespective of whether an indication of imminent ovulation has been obtained before all of said provided testing devices have been used.

Preferably, the user is directed to perform one test on day 6, and to use all of the remaining testing devices on a daily basis during the repeated testing period.

The invention also provides a kit for use in any of the methods as set forth above, comprising a plurality of disposable body fluid testing devices, together with means for reading and interpreting the results of tests performed using said testing devices.

The invention also encompasses a replenishment pack of disposable body fluid testing devices for use in any of the methods as set forth above, with directions to the user to use all of said contained disposable testing devices during the course of a single ovulation cycle. Preferably the pack contains not more than 12 testing devices, more

preferably at least 7 but not more than 10 devices.

By requiring the user to use all of a numerically-small single batch or set of disposable testing devices per cycle, there are advantages both for the user and for the manufacturer of the devices. The user benefits because the "monthly" testing schedule is simplified - there is no need for a decision to be taken on when to stop the repeated testing, or about using up during subsequent cycles testing devices left over from earlier cycles. For the manufacturer, there is assurance that data for each cycle is derived from a single batch of testing devices, thus eliminating problems of standardisation that might otherwise arise, and reducing the complexity of any monitor required to interpret the test data. No activity by the user is required to ensure calibration of the assays. The disposable testing devices can be supplied in standard "monthly" replenishment packs, streamlining the packaging operation. Because the problem of "leftover" testing devices is eliminated, one possible cause for customer enquiries is also avoided.

An advantage of the methods of the present invention is that effective monitoring of the ovulation cycle can be achieved using data derived solely from the measurement of body fluid analyte concentration(s). It is unnecessary to combine this data with other parameters. In particular, there is no need to supplement this data with routine measurement of basal body temperature.

By adopting a concentration reference value from data in the early part of the current cycle, the methods of the invention avoid the need for calibration and ensure that the base-line reference is personal to the subject under test. This leads to a clearer indication of the significant pre-ovulation concentration change, compared to previously proposed methods based on day-to-day

measurements.

The analyte chosen for providing the warning of imminent ovulation is not critical to the invention, provided that the analyte exhibits a detectable concentration change within the time interval between the commencement of testing (as determined herein) and a safe time in advance of actual ovulation in the current cycle.

The invention can be applied in any method of monitoring the status of a current ovulation cycle of an individual human female subject involving the measurement of a body fluid analyte of significance in relation to the status of ovulation cycle and which exhibits a detectable change during the pre-ovulation phase of the cycle occurring at least 2 and more preferably at least 3 days in advance of the day of actual ovulation.

The following description is provided, by way of example only, in relation to the urinary hormones E3G, luteinizing hormone (LH), and pregnanediol-3-glucuronide (P3G), although it will be readily appreciated that the principles of the method can be used in relation to other biochemical markers, for example the hormones estradiol and progesterone, found for example in the blood or in saliva. The method of the invention may be used in combination with observations of other physiological signs of the level of fertility in a female, of which she is aware, or can readily be made aware of, e.g. markers in other body fluids.

Ovulation day can be determined by any of the known chemical or physiological parameters, although a preferred method is by measuring the level of LH. Once the LH surge has been detected, it can be said that ovulation is imminent. Also, the day of the cycle on which ovulation has occurred can be noted for future reference. If the LH

surge is detected, and hence the day of ovulation accurately pinpointed, it can be indicated to the user with a very high degree of certainty that the subject will no longer be fertile four days hence (3 days after ovulation). For practical purposes, a urinary LH concentration of 20 mIU/ml can be regarded as a universal threshold indicative of the LH surge under virtually all circumstances.

The expression "LH surge" is used herein to mean the dramatic rise in LH concentration that precedes the event of ovulation. In the art, reference is made also to "LH max", i.e. the peak concentration of LH. In the majority of individuals, these are for all practical purposes simultaneous, when the cycle is monitored on a day-by-day basis. However, in a few individuals, perhaps 20% of the population, the actual peak concentration of LH is not observed until the day following the main concentration rise. For the purposes of the invention, we prefer to use the observable rise as the critical parameter.

Alternatively, or in addition, the end of the fertile phase can be declared on the basis of knowledge of the estradiol (or metabolite thereof) concentration, in the current cycle. Conveniently, this may be declared on a set day following a peak concentration value. Because the peak concentration of urinary E3G, for example, appears to be a less readily detectable event than the LH surge, the E3G "peak" may be defined by reference to a threshold value, determined for example by the relationship:

$$\frac{[i]}{[r]} > 2.5, \text{ preferably } \geq 3$$

the "peak" being taken to occur on the day when this relationship is first satisfied during the testing regime adopted in the current cycle. The inverse relationship

will apply if the E3G signal in inversely proportional to actual concentration. In some instances this may be the same day as the significant E3G rise indicative of imminent ovulation is detected. When the E3G "peak" has been detected, the fertile phase can be assumed to end on the sixth, or more safely the seventh or eighth, day later. In this embodiment, the invention provides the option of a method of monitoring fertility in the current cycle based solely on data derived from estradiol/metabolite assays.

Another method for predicting the end of the fertile period (though not so accurately the day of ovulation) is to measure the levels of the urinary hormone P3G. P3G has a relatively low level in urine until the start of the luteal phase, at which point its level rises fairly sharply. Therefore, once an elevated level of P3G is detected, it can be indicated to the user that the luteal phase of the cycle - ie. the terminal infertile period - has commenced. An elevated level of urinary P3G can be based on data taken during the current and/or one or more preceding cycles. An "elevated" P3G level can be recorded, for example, when either the level of P3G detected is greater than the sum of the four previous recorded levels of P3G in the same menstrual cycle, or greater than 3500 ng/ml, whichever of these two thresholds is lower and is first achieved. Once an "elevated" P3G level is recorded, the subject can be advised that she is infertile for the remainder of that cycle.

If desired, the detection of either LH or P3G can be used as a trigger to indicate that the subject is no longer fertile until the end of the cycle, with one hormone acting as a "back up" to the other. However, it is preferred that the detection of LH be used as a primary indicator of whether ovulation has or is about to occur, since the detection of LH lends itself to more accurate determination of the exact ovulation day than the use of P3G.

Methods of detecting body fluid analytes, such as urinary hormone metabolites, suitable for the purposes of this method, are well known to those skilled in the art. In a preferred embodiment, the analyte is detected by assay methods and devices as described in our UK patent GB 2204398 and our European patent application EP-A-383619, the contents of which are incorporated herein by reference.

Where the method of the invention relies on measurement of a urine component, this must be done on a urine sample. A variety of immunoassay techniques are available which enable urine components to be measured. A wide variety of solid phase testing devices such as dipsticks and chromatographic strips have been described in the literature, and can readily be adapted for use in determining urinary analytes. The device should at least be capable of indicating relative levels of analyte, eg. E3G, in threshold bands. Examples of simple assay technology that can readily be adapted for use in the home is described, for example, in EP 0225054, EP 0183442, EP 0186799 and GB 2204398, the disclosures of these specifications being incorporated herein by reference. Disposable assay strips such as those described in GB 2204398 which simply require to be contacted with urine and which provide an assay result in semi-qualitative form, eg. by means of a series of test zones on the strip which are progressively positive at higher urinary analyte levels, can be used. Multiple strips that respond at different analyte thresholds can be used, rather than a single strip. Alternatively, a visually readable quantitative assay can be based on progression of a visible, eg. coloured, region or "front" over a surface (eg. radial diffusion), using for example an enzyme-labelled assay.

In a more sophisticated embodiment of the invention, a recording device is provided which incorporates means for reading the result of the urine assay, eg. by measuring the

absorbance by or fluorescence from an assay strip. This may enable a more precise numerical indication to be given of the analyte level, and further enhance the accuracy of the method.

In an embodiment of the invention in which two or more analytes are measured simultaneously, such measurement can if desired be performed using a single body fluid testing device, eg. a device incorporating multiple assay strips, or a single strip capable of independently detecting the level of the different analytes.

The detailed electronics of a recording device capable of assimilating, remembering and handling analyte concentration data, as well as providing the preferred electronic features of the device discussed herein, and predicting future cycles on the basis of such data, can readily be provided by those skilled in the electronics art once they have been advised of the factors that such a device must take into consideration, and the information that the device must provide for the user. Such detailed electronics do not form part of the invention. However, by way of example only, the basic functions that may be required in such a device are outlined in Figure 3 of the accompanying drawings and described briefly below.

By way of example only, practical aspects of the invention are described below with reference to the accompanying drawings, of which:

Figure 1 of the accompanying drawings illustrates an ovulation cycle monitoring device for use in accordance with the invention, together with an associated urine sample testing device.

Figure 2 shows the urine testing device in greater detail.

Figure 3 shows, in schematic form, the basic functions that may be required in an electronic monitor for use in accordance with the invention.

Referring to Figure 1, the urine sample testing device comprises a flat elongate casing 100 having a locating means, represented by ridge 101 on its lower surface 102. Projecting from one end of the casing is a bibulous sample receiving member 103.

The monitor comprises a casing 110 having a recess 111 in its upper surface 112 to accommodate the casing 100 of the testing device. Recess 111 incorporates a locating slot 113 into which the locating ridge 101 on the casing of the testing device can be inserted to positively locate the testing device in relation to a reading window 114 in the recess. Casing 110 contains means (not shown) such as a fluorescence reader or optical density reader to measure the result of a urinary analyte concentration assay performed using the testing device, according to the labelling system chosen to reveal the assay result.

The sloping front face 115 of the monitor casing incorporates a large window 116 through which information can be conveyed to the user eg. by means of an LED display or other visual output. This information can be provided in a variety of forms, such as an indication of a calender and the need to perform urine tests, and an indication of the current status of the ovulation cycle. The sloping face 115 of the casing also incorporates a button 117 which the user can press to indicate the commencement of an ovulation cycle and to start the monitor processing information relative to that cycle.

Information can be conveyed to the user by means of a liquid crystal or LED display, for example. If desired, information on the state of fertility can be conveyed by a

simple visual indication, eg a combination of colours showing, for example, green for infertile and red for fertile. Optionally, another signal, e.g. yellow, for any intermediate stage when conception is less likely but still possible, may be shown. Especially if the device is intended primarily as an aid to contraception, it should "fail safe" by showing a "fertile" signal.

The invention further provides a kit for monitoring the ovulation cycle of a female mammal, comprising a monitoring device as set forth above, together with at least one testing device capable of being used to measure the level of one or more urine components. It is envisaged that the monitoring device will generally be of a relatively durable nature and capable of being used over a considerable number of cycles. The testing devices for measuring the urine components are preferably disposable after individual use, and it is therefore envisaged that the user of the monitoring device will need to replenish the testing devices.

In general the monitor will be battery-powered, and incorporates in side 118 of the casing an access point such as a removable cover 119 to permit batteries to be inserted and changed.

Referring to Figure 2, the testing device is shown inverted relative to the aspect seen in Figure 1. The locating ridge 101 is now on the upper surface 200. Also in the surface 200 now uppermost is a result window 201. The body of the testing device can incorporate an immunochromatograhic strip (not shown) incorporating all necessary reagents to enable an immunoassay to be formed which detects the presence and concentration of analyte in a urine sample applied to the sample collecting member 103. The result of the assay can be effected by the immobilization of a labelled component, via a sandwich or

competition reaction in the presence of analyte in an applied urine sample, the labelled reagent becoming concentrated in a zone revealed through the result window. When the testing device is inverted and located in the recess 111 in the casing of the monitor, the result window is immediately adjacent to the reading window 114 in the monitor and the assay result can be determined. For example, if the label is a fluorescent reagent, the reading means within the monitor can detect and measure fluorescent light output from the accumulated label in the detection zone on the strip to provide a numerically accurate concentration value for the analyte in the urine sample. This information can be processed by the monitor together with calender information resulting from the initiation of the cycle process by the user and historical data which the monitor can retain from previous cycles.

Referring to Figure 3, some of the basic elements which may be required in an electronic monitoring device are seen. The individual features can be entirely conventional, and those familiar with the art of electronics will appreciate that other combinations and arrangements of such features can be employed to achieve the objectives of the invention. For example, so-called "hard-wired" systems, and "neural networks", can be used in place of conventional microprocessors based on "chip" technology. As depicted in Figure 3, the combination essentially comprises:

A reading unit 300 to derive information from a test device, such as a test stick, the reading unit comprising an illuminator 301 and a reader 302 (represented here as a photo diode). The reading unit feeds into a conversion unit 303 to convert the optical signal into a form usable by a microprocessor 304. As an optional feature, a calibration system 305 is provided to convert the signal derived from the reading unit into data corresponding, for example, to an absolute concentration value. A timer, such

as a clock 306 is required to regulate measurements within a cycle. The microprocessor 304 processes, memorizes and interprets results in the light of previous events, particularly recorded from previous cycles. The user interface 307 will generally comprise at least means, such as a push button, which the user can operate at the commencement of a cycle to initiate the operation of the device as a whole. The power supply 308 should include means, such as a memory back up capacitator 309, to prevent loss of historical data if it becomes necessary to replace batteries.

Aspects of the invention are illustrated in the following Examples. These relate to the monitoring of the human ovulation cycle.

EXAMPLE 1

This example sets out a convenient algorithm on which a monitoring method in accordance with the invention can be based. The kit provided to the user comprises a plurality of dual-analyte disposable urine testing devices, capable of assaying urinary E3G and urinary LH in a form readable by a monitor also provided. The monitor can receive each used testing device and determine the urinary concentration of each analyte. This information is stored in the monitor and compared with similar data obtained on subsequent days in the same cycle. The monitor has a menstruation button that the user must press at the start of the cycle, and a display panel or the like to convey information about cycle status, and to indicate to the user when testing should be performed.

a) Algorithm rule structure

The objective is to:

i) identify the position of the LH surge in an individual cycle;

ii) identify a significant increase in E3G concentration in an individual cycle with respect to the E3G concentration on day 6 of that cycle.

The number of tests available each routine month is limited to 8, and a test strategy which will maximise the chances of achieving i) and ii) is adopted.

b) Start-up cycles

In order to establish an adequate initial data base, during the first cycle of use the monitor requires sixteen tests. This is to establish baseline data for the individual. The user presses the menstruation button on the monitor on the

morning after her menstruation begins. This day is recorded as day 1 by the monitor. Testing commences on day 8 and continues daily until day 23. This testing is targeted to maximise the chance of observing the LH surge.

At the start of cycle 2 and the start of all following cycles, the menstruation button is pressed as above. From cycle 2 onwards, eight tests only are used for each cycle. All eight tests must be from the same batch and all must be completed. In all cycles from cycle 2 onwards, testing commences on day 6. For cycles 2 and 3, tests two to eight are conducted on consecutive days starting on the typical LH surge day minus four days. From cycle 4 onwards, regarded as the first routine cycle, tests two to eight are conducted in sequence from typical LH surge minus five days. The typical LH surge day is defined as the mean day of LH surge for up to the previous six months.

c) Start of the fertile phase

In cycle 1, the monitor declares the woman fertile from day 6 onwards, as no information about cycle characteristics has been collected. In cycles 2 and 3, the monitor can use the typical position of the LH surge from the previous cycle(s) to determine the start of the fertile phase. However, because of the limited amount of cycle data available, the monitor will still declare a woman fertile during cycles 2 and 3 on day 6 or on typical LH surge minus 7 days, whichever is later.

In subsequent routine cycles, the onset of the fertile phase is set by detection of a significant change in the E3G signal with respect to day 6. When the ratio of the current day's signal for E3G (S_1) to the day 6 signal (S_6) reaches a set threshold as set forth above, the woman is declared fertile.

d) End of the fertile phase

In normal operation, the end of the fertile phase is defined as the fourth morning after the detection of the LH surge. In the absence of a detectable LH surge during the test sequence, the system declares the end of the fertile phase to be six days after the last test. The rationale for this calculation is as follows. The testing regime is designed to cover the typical position of the LH surge plus one day. Published WHO study data showed within-woman variability of LH surge position to be 1.8 days. Adding five days to the declared fertile period after testing has been completed allows two standard deviations confidence that the LH surge will occur within the assigned fertile period.

In non-normal operation (cycle 1), where the monitor has no information about the typical LH surge position, if this parameter is not detected, the end of the fertile phase is declared on cycle day 28.

EXAMPLE 2

This example uses representative E3G profiles from two women - one known to have low levels of urinary E3G and the other known to have relatively high levels. In the first two columns of each table, 30 days of each cycle are set out in terms of their fertility. The first phase is termed infertile and consists of that portion of the follicular phase during which unprotected intercourse would not be expected to result in conception, followed by a transitional phase during which changes occur that lead to a fertile state and during which a positive signal to indicate the onset of the fertile phase is required. The fertile phase is that phase before and after ovulation during which unprotected intercourse is most likely to

result in conception. Its duration before ovulation is dictated entirely by the effective lifetime of sperm, and this, in turn is influenced by factors controlled by the female hormones, especially mucus. The post fertile, luteal phase is that time after which the ovum has left the uterus and conception in the current cycle is no longer possible.

E3G values are given in the third column. These were derived by immunoassay on early morning urine samples collected each day. The immunoassay was a conventional enzyme-labelled-antigen competitive assay. The values given are in ng/ml.

Actual ovulation is taken as 24 hours following the LH surge. These LH values were determined by conventional enzyme-labelled sandwich immunoassay on the same samples, but the values are not included in the table as ovulation date is the essential result.

The algorithm of Example 1 has been applied to each cycle, taking the E3G trigger point as:

$$\frac{[i]}{[\text{day } 6]} \geq 2$$

INDIVIDUAL A

CYCLE A 1: Start-up cycle

Day	Test	Phase	E3G value	"Red" status	Actual ovulation
1		infertile			
2		"			
3		"			
4		"			
5		"			
6		"		***	
7		"		***	
8	*	"	1.9	***	
9	*	"	3.1	***	
10	*	"	5.4	***	
11	*	"	2.1	***	
12	*	"	5.3	***	
13	*	"	10.5	***	
14	*	"	7.7	***	
15	*	fertile	5.2	***	
16	*	"	8.3	***	
17	*	"	6.8	***	
18	*	"	4.3	***	LHS + 1
19	*	"	4.9	***	
20	*	"	5.3	***	
21	*	postfertile	3.3		
22	*	"	4.9		
23	*	"	6.2		
24		"			
25		"			
26		"			
27		"			
28		"			
29		"			
30		"			

LH surge was on day 17, therefore repeated testing to commence on day 13 in next cycle.

CYCLE A 2

Day	Test	Phase	E3G value	"Red" Status	Actual Ovulation
1		infertile			
2		"			
3		"			
4		"			
5		"			
6	*	"	3.5		
7		"			
8		"			
9		"		***	
10		"		***	
11		"		***	
12		"		***	
13	*	"	8.9	***	
14	*	fertile	14.6	***	
15	*	"	12.6	***	
16	*	"	8.8	***	
17	*	"	15.8	***	LHS + 1
18	*	"	6.9	***	
19	*	"	6.5	***	
20		postfertile			
21		"			
22		"			
23		"			
24		"			
25		"			
26		"			
27		"			
28		"			
29		"			
30		"			

Mean LHS of cycles A1 and A2 is day "16.5", therefore repeated testing to commence on day 12 in next cycle.

CYCLE A 3

Day	Test	Phase	E3G value	"Red" Status	Actual Ovulation
1		infertile			
2		"			
3		"			
4		"			
5		"			
6	*	"	1.6		
7		"			
8		"		***	
9		"		***	
10		"		***	
11		"		***	
12	*	fertile	6.2	***	
13	*	"	23.6	***	
14	*	"	21.3	***	
15	*	"	8.3	***	LHS + 1
16	*	"	4.5	***	
17	*	"	3.7	***	
18	*	postfertile	3.4		
19		"			
20		"			
21		"			
22		"			
23		"			
24		"			
25		"			
26		"			
27		"			
28		"			
29		"			
30		"			

Mean LHS from cycles A1 to A3: day "15.7". Repeated testing commencement day for first routine cycle: day 10.

CYCLE A 4

First routine cycle

Day	Test	Phase	E3G value	"Red" Status	Actual Ovulation
1		infertile			
2		"			
3		"			
4		"			
5		"			
6	*	"	3.1		
7		"			
8		"			
9		"			
10	*	"	6.1		
11	*	fertile	16.7	***	
12	*	"	10.8	***	
13	*	"	22.8	***	
14	*	"	21.3	***	LHS + 1
15	*	"	9.4	***	
16	*	"	12.2	***	
17		postfertile			
18		"			
19		"			
20		"			
21		"			
22		"			
23		"			
24		"			
25		"			
26		"			
27		"			
28		"			
29		"			
30		"			

Days warning of actual ovulation: 3

Mean LHS from cycles A1 to A4: day "15.3".

Repeated testing commencement day for next cycle: day 10.

CYCLE A 5

Second routine cycle

Day	Test	Phase	E3G value	"Red" Status	Actual Ovulation
1		infertile			
2		"			
3		"			
4		"			
5		"			
6	*	"	4.8		
7		"			
8		"			
9		"			
10	*	"	8.5		
11	*	"	7.3		
12	*	"	6.3		
13	*	"	7.0		
14	*	fertile	11.8	***	
15	*	"	19.3	***	
16	*	"	18.5	***	
17		"		***	LHS + 1
18		"		***	
19		"		***	
20		postfertile			
21		"			
22		"			
23		"			
24		"			
25		"			
26		"			
27		"			
28		"			
29		"			
30		"			

Days warning of actual ovulation: 3

Mean LHS from cycles A1 to A5: day "15.4".

Repeated testing commencement day for next cycle: day 10.

INDIVIDUAL B

CYCLE B1: Start-up cycle

Day	Test	Phase	E3G value	"Red" Status	Actual Ovulation
1		infertile			
2		"			
3		"			
4		"			
5		"			
6		"		***	
7		"		***	
8	*	"	25.1	***	
9	*	"	10.1	***	
10	*	"	16.8	***	
11	*	"	28.2	***	
12	*	"	24.6	***	
13	*	"	28.7	***	
14	*	"	27.7	***	
15	*	"	62.6	***	
16	*	"	68.5	***	
17	*	fertile	61.9	***	
18	*	"	103.4	***	
19	*	"	85.4	***	
20	*	"	45.4	***	LHS + 1
21	*	"	14.9	***	
22	*	"	46.6	***	
23	*	postfertile	49.3		
24		"			
25		"			
26		"			
27		"			
28		"			
29		"			
30		"			

LH surge was on day 19, therefore repeated testing to commence on day 15 in next cycle.

CYCLE B 2

Day	Test	Phase	E3G value	"Red" Status	Actual Ovulation
1		infertile			
2		"			
3		"			
4		"			
5		"			
6	*	"	28.9		
7		"			
8		"			
9		"			
10		"			
11		"			
12		"		***	
13		"		***	
14		"		***	
15	*	fertile	62.0	***	
16	*	"	94.6	***	
17	*	"	58.4	***	LHS + 1
18	*	"	42.4	***	
19	*	"	60.4	***	
20	*	"	56.0	***	
21	*	postfertile	35.0		
22		"			
23		"			
24		"			
25		"			
26		"			
27		"			
28		"			
29		"			
30		"			

Mean LHS from cycles B1 and B2 is day "17.5", therefore repeated testing to commence on day 13 in next cycle.

CYCLE B 3

Day	Test	Phase	E3G value	"Red" Status	Actual Ovulation
1		infertile			
2		"			
3		"			
4		"			
5		"			
6	*	"	17.2		
7		"			
8		"			
9		"			
10		"		***	
11		"		***	
12		"		***	
13	*	"	23.9	***	
14	*	fertile	63.8	***	
15	*	"	22.1	***	
16	*	"	65.9	***	
17	*	"	41.2	***	LHS + 1
18	*	"	7.6	***	
19	*	"	35.3	***	
20		postfertile			
21		"			
22		"			
23		"			
24		"			
25		"			
26		"			
27		"			
28		"			
29		"			
30		"			

Mean LHS from cycles B1 to B3: day 17.

Repeated testing commencement day for first routine cycle: day 12.

CYCLE B 4

First routine cycle

Day	Test	Phase	E3G value	"Red" Status	Actual Ovulation
1		infertile			
2		"			
3		"			
4		"			
5		"			
6	*	"	12.9		
7		"			
8		"			
9		"			
10		"			
11		"			
12	*	"	38.3	***	
13	*	fertile	70.6	***	
14	*	"	74.6	***	
15	*	"	70.6	***	
16	*	"	49.7	***	LHS + 1
17	*	"	23.5	***	
18	*	"	29.8	***	
19		postfertile			
20		"			
21		"			
22		"			
23		"			
24		"			
25		"			
26		"			
27		"			
28		"			
29		"			
30		"			

Days warning of actual ovulation: 4

Mean LHS from cycles B1 to B4: day "16.5".

Repeated testing commencement day for next cycle: day 11.

CYCLE B 5

Second routine cycle

Day	Test	Phase	E3G value	"Red" Status	Actual Ovulation
1		infertile			
2		"			
3		"			
4		"			
5		"			
6	*	"	7.2		
7		"			
8		"			
9		"			
10		"			
11	*	"	14.1		
12	*	"	17.4		
13	*	"	41.3	***	
14	*	"	57.5	***	
15	*	fertile	42.0	***	
16	*	"	55.4	***	
17	*	"	60.1	***	
18		"		***	LHS + 1
19		"		***	
20		"		***	
21		postfertile			
22		"			
23		"			
24		"			
25		"			
26		"			
27		"			
28		"			
29		"			
30		"			

Days warning of actual ovulation: 5

LHS detected on last day at testing. Mean LHS from cycles B1 to B5: day "16.6".

Repeated testing commencement day for next cycle: day 11.

EXAMPLE 3

This example illustrates a very simple but convenient human contraceptive system, relying solely per cycle on a limited number of assays for the urinary analyte E3G.

The user is provided with a 'monthly' batch of 8 identical disposable assay devices, each comprising an assay strip to which a urine sample can be applied, the strip including all necessary reagents to enable a signal indicative of the E3G concentration to be provided, for example by a competition reaction involving a labelled specific binding reagent which becomes bound in a detection zone on the strip in an amount directly or inversely proportional to the E3G concentration in the urine sample. An optical electronic reader is also provided, which converts signal information from the used strip into numerical data and processes this data to provide the user with appropriate information concerning cycle status.

An initial urine assay is performed on day 6 of the current cycle (day 1 being the day on which menese is first observed), to establish a base reference for the E3G concentration in this cycle.

A second urine assay is performed on day 9, and each day thereafter, until either all tests are used up, or until an indication of an elevated E3G concentration indicative of imminent ovulation is given. A sufficiently elevated E3G concentration is declared when the ratio of the reference concentration [r] to the test concentration [i] first meets the criterion:

$$\frac{[i]}{[r]} \geq 2$$

in the case of direct proportionality between the test signal and the E3G concentration, or

$$\frac{[r]}{[i]} \geq 2$$

in the case of inverse proportionality.

Unprotected intercourse is avoided on the day the sufficiently elevated E3G concentration is detected, and for 12 immediately successive days thereafter.

If a sufficiently elevated E3G concentration is not detected before all of the tests have been used, unprotected intercourse is avoided for 15 immediately successive days following the last test day.

Conception does not occur.

This example provides the benefit to the user that only a few tests are required per month. Manufacturing simplicity is also provided, because only one analyte (E3G) is assayed.

If desired, the assay can be made more sophisticated, for example by enabling the event of ovulation to be detected by including urinary LH concentration data, and by pooling data from previous cycles, so that the abstinence period may be reduced further without increasing the likelihood of conception, as described generally hereinbefore.

CLAIMS:

1. A method of monitoring the fertility status of an individual female mammalian subject, involving testing of the body fluid concentration of an analyte, especially estradiol or a metabolite thereof, in which method said testing is conducted at least once during the interval spanning days 1 to 7 inclusive of the current cycle, to establish a reference concentration value or signal for the current cycle, and said testing is also conducted later in the current cycle and the concentration value or signal then obtained is compared to the reference value or signal.

2. A method of monitoring the current fertility status of an individual human female, involving testing of the body fluid concentration of estradiol or a metabolite thereof and comparing the test result with a reference value or signal to ascertain whether an elevated concentration indicative of imminent ovulation is present, wherein the reference value or signal for the current ovulation cycle is established by testing the body fluid concentration in the same individual at least once during the interval spanning days 1 to 7 inclusive of the current cycle.

3. A method of monitoring the fertility status of an individual female mammalian subject, involving testing of the body fluid concentration of at least one analyte of significance in relation to the status of the ovulation cycle during the pre-ovulation phase, wherein testing for said analyte is conducted at least once during the interval spanning days 1 to 7 inclusive of the current cycle calculated from the onset of menses, to establish a reference concentration value or signal for said analyte in the current cycle, and thereafter testing is conducted at least once prior to a day on which ovulation is likely to occur during the cycle, analyte concentration values or signals obtained during said later testing being compared

with the reference concentration value or signal to determine whether a concentration change indicative of imminent ovulation is occurring or has occurred since the previous test.

4. A method of monitoring the fertility status of an individual female mammalian subject, involving testing of the body fluid concentration of at least one analyte of significance in relation to the status of the ovulation cycle during the pre-ovulation phase, wherein testing for said analyte is conducted at least once during the interval spanning days 1 to 7 inclusive calculated from the onset of menses, to establish a reference concentration value or signal for said analyte in the current cycle, and then teesting is conducted at least once (preferably daily) during a period of days commencing at least 5, preferably at least 6, numerical days in advance of the mean numerical day on which actual ovulation has occurred over one or more previous ovulation cycles in the same individual subject, analyte concentration values or signals obtained during said period of days being compared with the reference concentration value or signal to determine whether a concentration change indicative of imminent ovulation is occurring or has occurred since the previous test.

5. A method according to any one of the preceding claims, wherein said concentration reference value is established from a single test.

6. A method according to any one of the preceding claims, wherein said concentration reference value is established from test(s) conducted during the interval spanning days 4 to 7 inclusive.

7. A method according to claim 6, wherein said concentration reference value is established from test(s) conducted on day 5 and/or day 6.

8. A method according to claim 5, wherein the single test is conducted on day 6.

9. A method according to any one of the preceding claims, wherein said subject is human.

10. A method according to any one of the preceding claims, wherein the body fluid is urine.

11. A method according to any one of the preceding claims, wherein the analyte is estradiol or a metabolite thereof, such as E3G.

12. A method according to claim 11, wherein a significant difference between the analyte reference concentration value [r] and a test value [i], indicative of imminent ovulation, is taken to be:

$$1.5 \leq \frac{[i]}{[r]} \leq 2.5$$

in the case of direct proportionality between the test signal and analyte concentration, or the inverse in the case of inverse proportionality between the test signal and analyte concentration.

13. A method according to claim 12, wherein the analyte is E3G, and the significant difference in E3G concentration [i] indicative of imminent ovulation is taken to be:

$$\frac{[i]}{[r]} \geq 2$$

in the case of direct proportionality between the test signal and E3G concentration, or the inverse in the case of inverse proportionality between the test signal and E3G concentration.

14. A method according to any one of the preceding claims, wherein the body fluid concentration of LH is determined to identify the actual ovulation day in the current cycle.

15. A method according to any one of the preceding claims, wherein the mean ovulation day is derived from data collected during at least 3 consecutive previous cycles.

16. A method according to any one of the preceding claims, wherein the mean ovulation day is derived from data collected during at least 5 consecutive previous cycles.

17. A method according to any one of the preceding claims, wherein the mean ovulation day is derived from data obtained during at least the immediately preceding cycle.

18. A method according to claim 17, wherein the mean ovulation day is derived from data obtained from a rolling reference base consisting of a fixed number of consecutive cycles immediately preceding the current cycle.

19. A method according to claim 18, wherein the rolling reference base consists of the immediately preceding 3 to 12 cycles.

20. A method according to claim 18, wherein the rolling reference base consists of the immediately preceding 5 or 6 cycles.

21. A method according to any one of the preceding claims, wherein the end of the fertile phase is declared from knowledge of the LH surge in the current cycle.

22. A method according to claim 21, wherein the end of the fertile phase is taken to occur on the fourth day following LH surge detection.

23. A method according to any one of the preceding claims, wherein the end of the fertile phase is declared from knowledge of the concentration of estradiol or a metabolite thereof in the current cycle.

24. A method according to any one of the preceding claims, wherein the end of the fertile phase is declared from knowledge of the peak concentration of estradiol or a metabolite thereof in the current cycle, this peak being defined as the first occasion in the cycle when

$$\frac{[i]}{[r]} > 2.5, \text{ preferably } \geq 3,$$

is detected in the case of direct proportionality between the test signal and estradiol/metabolite concentration, or the inverse in the case of inverse proportionality between the test signal and estradiol/metabolite concentration.

25. A method according to claim 24, wherein the end of the fertile phase is taken to occur on the eighth day following the estradiol/metabolite peak detection.

26. A method according to any one of the preceding claims based solely on estradiol/metabolite assays.

27. A method according to any one of the preceding claims, which does not utilise the measurement of basal body temperature.

28. A method according to any one of the preceding claims, solely utilising body fluid analyte concentration data.

29. A method according to any one of claims 1 to 20, involving:

a) providing the user with a plurality of disposable body

fluid testing devices, said plurality being at least 7 but not greater than 12; and

b) directing the user to use all of said provided testing devices during a single ovulation cycle, in accordance with a predetermined testing schedule, irrespective of whether an indication of imminent ovulation has been obtained before all of said provided testing devices have been used.

30. A method according to claim 22, wherein the user is directed to perform one test on day 6, and to use all of the remaining testing devices on a daily basis during the repeated testing period.

31. A method of monitoring the fertility status of an individual female mammalian (generally human) subject, involving testing of the body fluid concentration of at least one analyte of significance in relation to the status of the ovulation cycle during the pre-ovulation phase, wherein

a) the user is provided with a plurality of disposable body fluid testing devices, said plurality preferably being at least 7, but preferably not greater than 12; and

b) the user is directed to use all of said provided testing devices during a single ovulation cycle, in accordance with a predetermined testing schedule, irrespective of whether an indication of imminent ovulation has been obtained before all of said provided testing devices have been used.

32. A kit for use in a method according to any one of the preceding claims comprising a plurality of disposable body fluid testing devices, together with means for reading and interpreting the results of tests performed using said testing devices.

33. A replenishment pack of disposable body fluid testing devices for use in a method according to any one of the preceding claims, with directions to the user to use all of said contained testing devices during the course of a single ovulation cycle.

34. A replenishment pack according to claim 33, containing not more than 12 disposable body fluid testing devices.

35. A replenishment pack according to claim 33, containing from 7 to 10 disposable body fluid testing devices.

36. A method of monitoring the current fertility status of an individual human female, involving testing of the body fluid concentration of estradiol or a metabolite thereof and comparing the test result with a reference value or signal to ascertain whether an elevated concentration indicative of imminent ovulation is present, wherein the reference value or signal for the current cycle is established by testing the body fluid concentration in the same individual at least once during the interval spanning days 4 to 7 inclusive, preferably on days 5 and/or 6, of the current cycle, testing is recommenced on day 9 of the current cycle and continued thereafter on at least a daily basis at least until a significantly elevated concentration is detected, and the status of the current cycle is declared to be "fertile" for the interval commencing on the day of significantly elevated concentration detection and for at least the immediately successive 12 days or until evidence of cycle termination is obtained, whichever occurs earlier.

37. A method according to claim 38, wherein if a significantly elevated concentration is not detected on or before day 15, the cycle is declared "fertile" for the interval lasting for at least 14, preferably 15, days immediately following day 15, or until evidence of cycle

termination is obtained, if this occurs earlier.

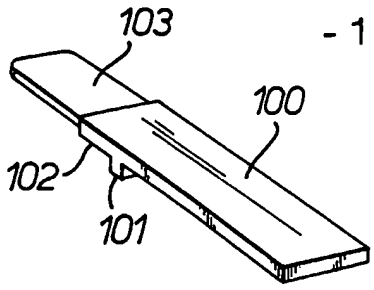
38. A human contraception method, involving:

a) testing the urinary concentration of estradiol or a metabolite thereof in the female partner at least once during the interval spanning days 4 to 7 inclusive, preferably on days 5 and/or 6, of the current cycle to establish a reference value or signal for the current cycle;

b) testing the urinary concentration again on an at least daily basis commencing on day 9 of the current cycle and continuing until day 15 (preferably day 14) of the current cycle; and

c) avoiding unprotected intercourse during the interval lasting for at least 12 days immediately following the day on which a significantly elevated urinary concentration is detected or, if a significantly elevated urinary concentration is not detected by day 15 (preferably day 14), avoiding unprotected intercourse during the interval lasting for at least 14, preferably 15, days immediately following day 15 (preferably day 14), in either case the interval optionally being terminated earlier in the event of evidence of cycle termination being obtained.

39. A method according to any one of claims 1, 2, 3 or 4, substantially as hereinbefore described.


103
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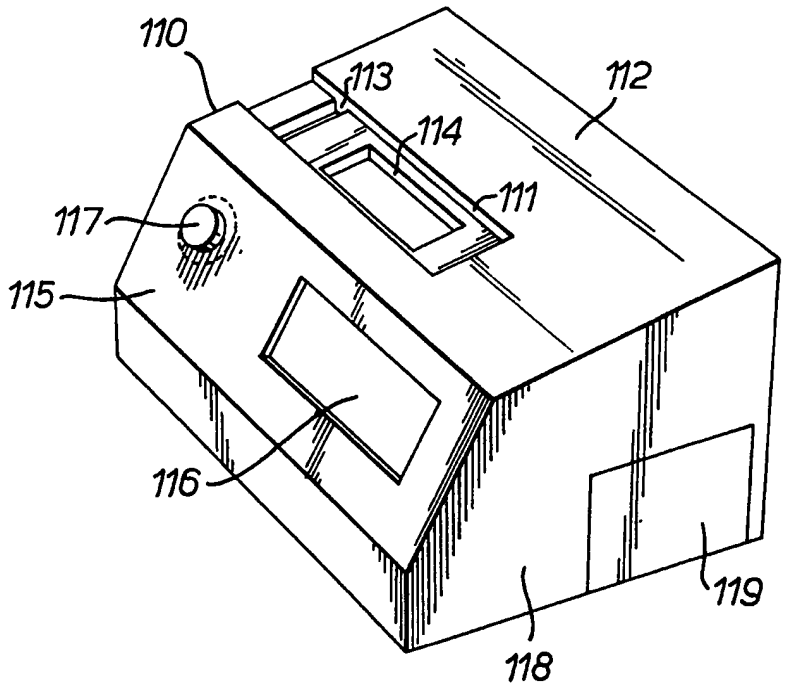
102
101

Fig. 1.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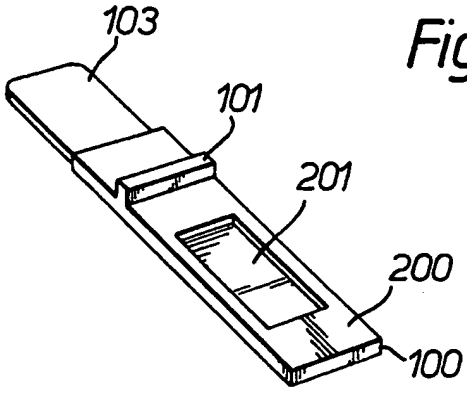
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Fig. 2.

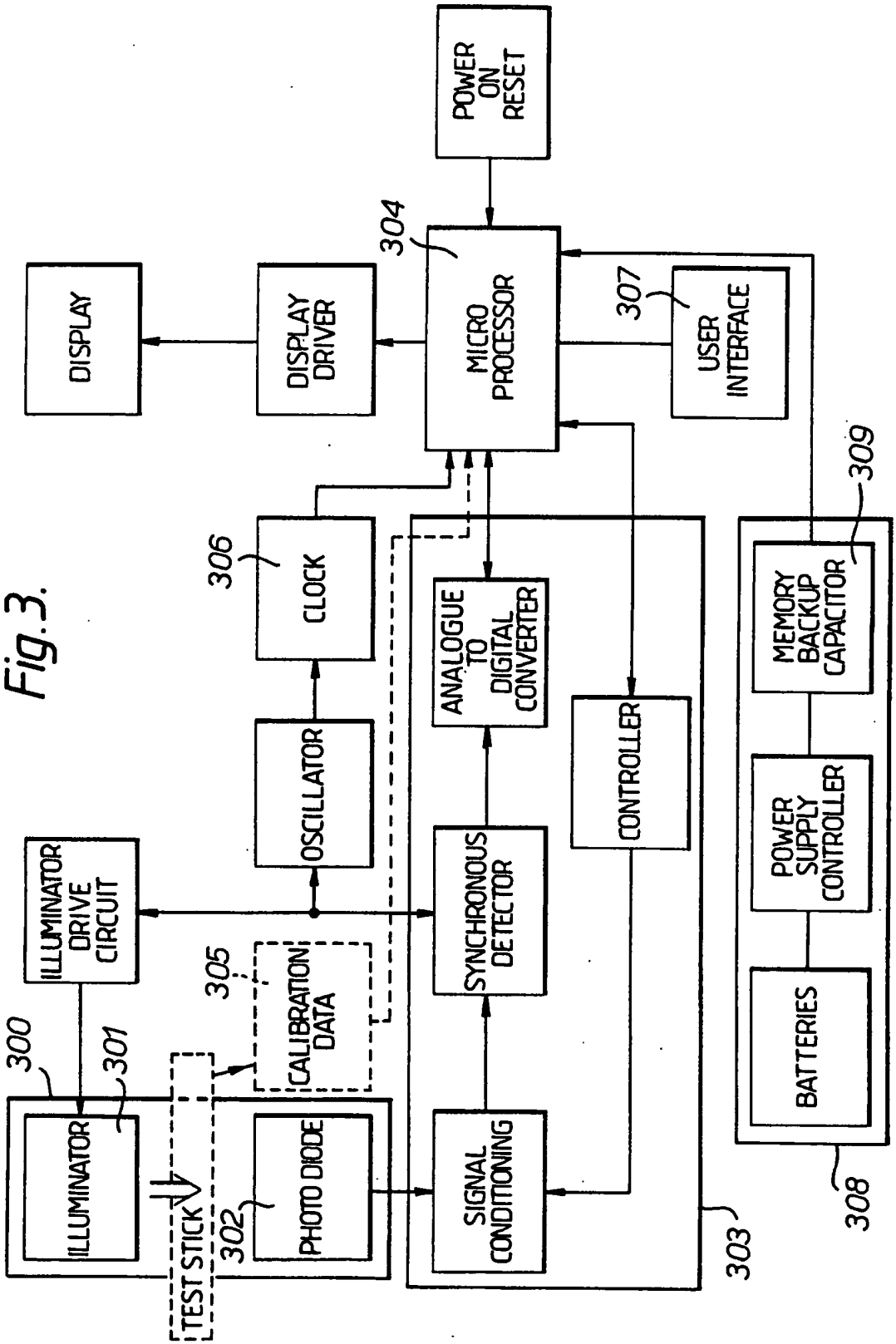
POWER ON RESET
304
MICRO PROCESSOR
DISPLAY
DISPLAY DRIVER
307
USER INTERFACE
306
CLOCK
309
MEMORY BACKUP CAPACITOR
ANALOGUE TO DIGITAL CONVERTER
OSCILLATOR
CONTROLLER
POWER SUPPLY CONTROLLER
ILLUMINATOR DRIVE CIRCUIT
SYNCHRONOUS DETECTOR
305
CALIBRATION DATA
300
301
BATTERIES
ILLUMINATOR
PHOTO DIODE
SIGNAL CONDITIONING
TEST STICK
302
303
308

Fig. 3.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 94/02068

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61B10/00 //G01N33/76,G01N33/74

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61B G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 385 621 (UNILEVER PLC) 5 September 1990 cited in the application see the whole document	1-11,14, 21-23, 31-33, 36-39
A	---	15-20, 25,28-30
X	US,A,4 151 833 (POLISHUK) 1 May 1979 cited in the application see column 2, line 6 - line 24; figure 8	3,4,6,9, 27-29, 31-33
A	--- US,A,5 043 888 (URIARTE) 27 August 1991 see abstract	15-20
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 October 1994	27. 10. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Ceder, O

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	'Proc Xth Int'l Congress on Fertility and Sterility' 1981 , MTB LTD cited in the application Collins et al. : see page 19 - page 33 ---	
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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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